Table II—^{13}C-NMR Data

Assignment	δ^a	Multiplicity
C-2	157.3 (169.5[b], 156.7[c])	Unresolved multiplet
C-4	171.6 (188.8[b], 172.0[c])	Triplet, $^2J_{CH}$ = 5 Hz
C-5	51.1 (56.4[b], 54.1[c])	Triplet, $^1J_{CH}$ = 147 Hz
C-6	30.3 (30.2[b], 31.2[c])	Quartet, $^1J_{CH}$ = 140 Hz
C-8	160.8	Singlet
C-1′	142.3	Broad doublet, $^3J_{CH} \simeq 9$ Hz
C-2′	118.1	Doublet of 1:3:3:1 quartets $^1J_{CH}$ = 168 Hz; $^3J_{CH\text{-}4'} \simeq {}^3J_{CH\text{-}6'} \simeq {}^3J_{CH\text{-}9} \simeq 5$ Hz
C-3′	133.2	Doublet of unresolved multiplets, $^3J_{CH} \simeq 11$ Hz
C-4′	121.5	Doublet of quartets, $^1J_{CH}$ = 168.5 Hz, $^3J_{CH} \simeq 6$ and 8 Hz
C-5′	130.3	Doublet, $^1J_{CH}$ = 163 Hz
C-6′	117.1	Doublet of unresolved multiplets, $^1J_{CH}$ = 165 Hz

[a] Chemical shifts in parts per million relative to tetramethylsilane. [b] Values of 2-amino-1,5-dihydro-1-methyl-4*H*-imidazol-4- one. [c] Values for its corresponding monohydrochloride.

more, these decouplings, apart from the collapse of C-5 and methyl carbon resonances, have weak effects on the aromatic carbon resonances, and the splittings due to small C—H couplings are still observable.

The assignment of 142.2 and 133.2 ppm resonances was made by comparison with similar compounds. Assuming that the substituent effects on the shifts of the aromatic carbons are additive and using the data reported previously (4) for the chlorine atom, the values calculated for the ureido group are very close to those determined for other aromatic ureas (5) and acetanilide (4).

The chemical shifts of C-2, C-4, C-5, and C-6 are close to those of 2-amino-1,5-dihydro-1-methyl-4*H*-imidazol-4-one hydrochloride in $^2H_6$-dimethyl sulfoxide (Table II) (6). The ureido ^{13}C-chemical shift (160.8 ppm) is nearer to urea (160.5 ppm) (7) than diphenylurea (152.7 ppm) or di-*p*-anisylurea (153.0 ppm) (5).

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Dissolution Profiles for Finely Divided Drug Suspensions

JOHN W. MAUGER ˣ, STEPHEN A. HOWARD, and KIRIT AMIN

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Abstract □ A suspension of micronized prednisolone acetate was separated into four fractions by the technique of centrifugal elutriation. Data showed that each fraction had a narrow particle size. The dissolution experiments were carried out under sink conditions (<10% of saturation concentration) in a dissolution apparatus with a rotating filter assembly and a continuous circulation of filtered fluid samples through a recording spectrophotometer. The dissolution profile was highly reproducible and substantially different for each fraction. As expected, fractions with the smallest and largest particles showed the fastest and slowest dissolution, respectively. Almost the entire dissolution profiles for four small particle size fractions can be satisfactorily described by the Higuchi–Hiestand model with the dissolution rate constant, K, in the range of 1.5–2.0 × 10^{-9}cm^2/sec. This is ~3.5 times greater than the value for K calculated on the basis of reported reasonable values for diffusion coefficient, density, and solubility.

Keyphrases □ Dissolution—profiles for drug suspensions, prednisolone acetate, centrifugal elutriation □ Drug suspensions—dissolution profiles, prednisolone acetate, centrifugal elutriation □ Prednisolone acetate—dissolution profiles for drug suspensions, centrifugal elutriation

Dissolution models for multisized drug particles have been proposed and studied experimentally. However, few studies deal specifically with finely divided drug particles (micrometer range). There were notable exceptions (1, 2) published more than a decade ago which showed approximate agreement between diffusional model theory and experimental data for micronized methylprednisolone particles. A more recent study (3) of the dissolution kinetics of micronized steroid particles was unable to confirm the application of the diffusion-based law for the decay of particle size used in those earlier studies (1, 2). To date, the relationship between diffusional-based dissolution theory for finely divided drug particles, and its experimental justification remains fragile.

One of the reasons for the inability to relate the theory with experimental data may be the difficulties encountered in obtaining very small particles with known narrow particle size distributions. The aforementioned studies used multisized drug particle populations in which the dissolution kinetics for the largest and smallest particles may have differed. This possibility has been discussed (4) and an interpolation formula provided which mixes the diffusion kinetics for large and small particles. Therefore, the possibility of mixed models makes critical testing of a specific model difficult. With recent advances in centrifugal elutriation separation and particle size measurement techniques (5) in conjunction with the spin filter dissolution apparatus, it has become possible to test the dissolution models with more rigorously controlled experiments.

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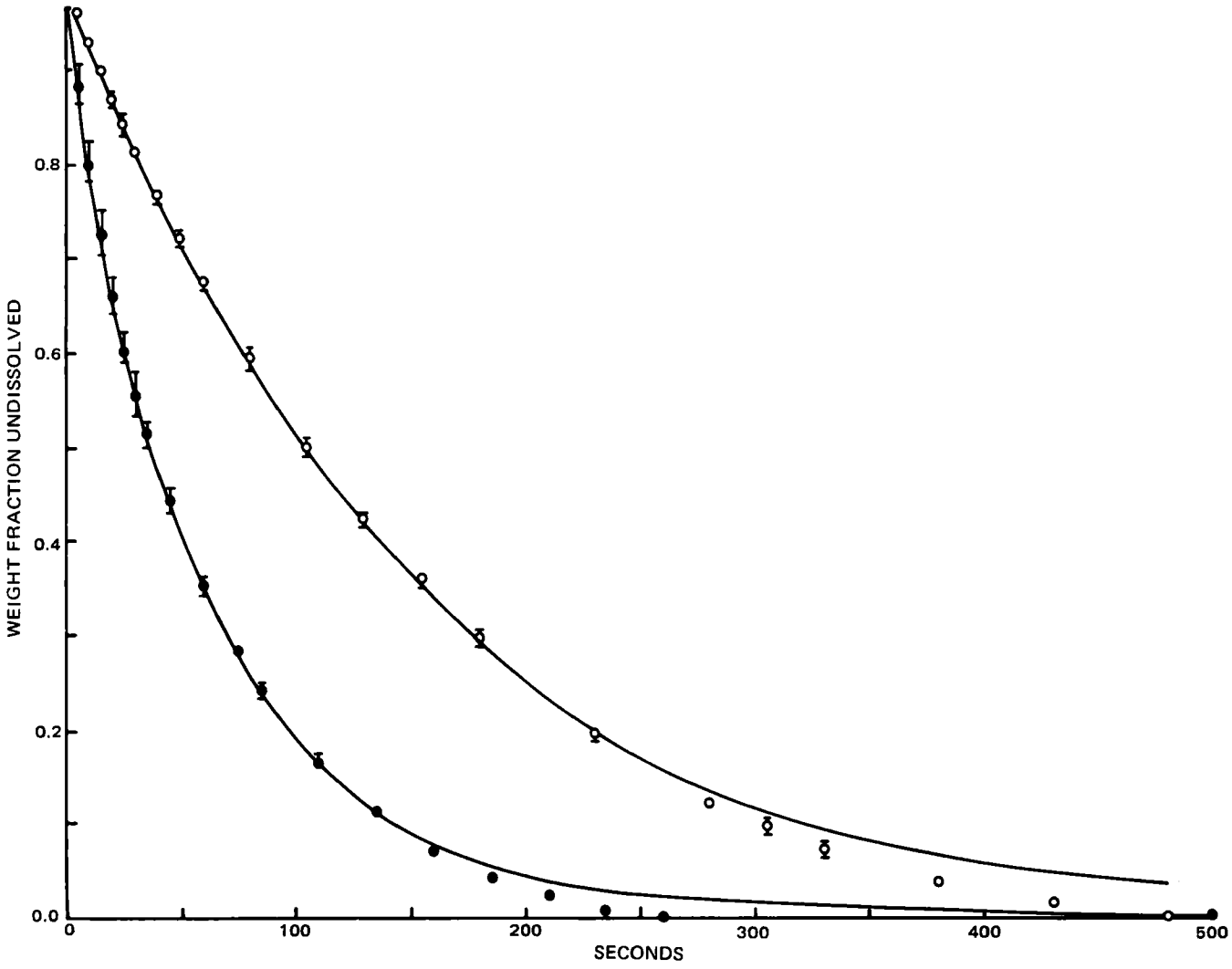

Figure 1—*Dissolution profiles for first and second prednisolone acetate fractions. Key: (●) experimental values for fraction 1, solid line calculated using theory with* K = 1.85×10^{-9} *cm²/sec; (○) experimental values for fraction 2, calculated using theory with* K = 1.50×10^{-9} *cm²/sec.*

EXPERIMENTAL

Particle Separation—A previous study (5) demonstrated that centrifugal elutriation[1,2] is capable of separating fractions of small particles with very narrow particle size distributions. In this study a 0.6% suspension of micronized prednisolone acetate in 0.9% sodium chloride solution presaturated with drug was separated into four fractions by the technique of centrifugal elutriation. Four fractions were obtained. Pump speeds of 30 and 52 ml/min and centrifuge speeds of 2000, 1000, and 500 rpm were utilized.

Particle Sizing—An electronic particle sizing device[3] with either a 50- or 200-μm aperture tube was used for particle size analysis. An electrolyte solution[4] presaturated with micronized prednisolone acetate was used as a vehicle. This multichannel instrument provides detailed information about particle size distribution. The particles were classified and counted into one of 14 channels. The first two channels were not used. Almost all of the particles in each fraction were distributed over not more than three to four consecutive channels indicating a narrow particle size distribution.

Dissolution—All dissolution experiments were carried out in an apparatus reported previously (6) which is well-suited for monitoring the dissolution of suspended particles. The rotating filter assembly used in this device provides a variable intensity of mild liquid agitation, and it also functions as an *in situ* nonclogging filter to allow continuous filtration of the dissolution fluid without removing the dissolving particles during the dissolution process.

Procedure—A prednisolone acetate suspension was prepared and elutriated as described, and then a measured sample of each fraction was dissolved in water for 24 hr and assayed. The concentrations thus obtained were utilized in adjusting the suspension concentration of each fraction so that a 5-ml sample would allow for perfect sink conditions to exist in the dissolution test.

Immediately prior to dissolution testing the sample was sized electronically as described, and within 5 min of sizing dissolution testing was initiated. The dissolution experiments were initiated by injecting 5 ml of the desired fraction of prednisolone acetate suspension in a liter of distilled water. The temperature was maintained at 37° and the stirring speed of the filter assembly was set at 600 rpm. Filtered fluid samples were continuously circulated through a spectrophotometer[5] and back into the dissolution flask at the rate of 100 ml/min. The absorbance at 247 nm was continuously recorded as a function of time. The final concentration of prednisolone acetate in the dissolution medium was kept below 10% of saturation.

RESULTS

Four size fractions of prednisolone acetate were obtained, sized, and dissolution tested. The results were then compared to the multisize form of the Higuchi–Hiestand model (1). Weight fraction remaining undissolved, $W(F)$, as a function of time, t, was calculated from the dissolution data in the following manner. The time scale was first corrected for the lag time by subtracting lag time (~15 sec), and the absorbances were corrected by subtracting absorbance due to dilution of the saturated solution (5 ml of saturated solution used in the dissolution experiment).

[1] Model JEG, Beckman Instrument Co., Fullerton, Calif.
[2] Model J-21B, Beckman Instrument Co., Fullerton, Calif.
[3] Model TAII, Coulter Electronics, Hialeah, Fla.
[4] Isoton, Coulter Diagnostics Inc., Hialeah, Fla.
[5] Cary 118, Varian Instruments, Palo Alto, Calif.

Table I—Particle Size Distributions for Fractions 1 and 2 with 50-μm Aperture Tube

Channel No. I	Diameter, μm	Fraction of Total Volume, F_I 1	2
3	0.897	0.0310	0.0094
4	1.130	0.0182	0.0045
5	1.425	0.0298	0.0049
6	1.795	0.0315	0.0052
7	2.260	0.0408	0.0084
8	2.845	0.0597	0.0114
9	3.585	0.1178	0.0218
10	4.520	0.2214	0.0709
11	5.695	0.2617	0.2373
12	7.175	0.1375	0.3693
13	9.040	0.0380	0.1915
14	11.390	0.0083	0.0426
15	14.350	0.0049	0.0062
16	18.100	0.0026	0.0166

Table II—Particle Size Distributions for Fractions 3 and 4 with 200-μm Aperture Tube

Channel No. I	Diameter, μm	Fraction of Total Volume, F_I 3	4
3	3.58	0.0087	0.0058
4	4.52	0.0168	0.0103
5	5.69	0.0502	0.0321
6	7.17	0.1549	0.0690
7	9.04	0.2907	0.1508
8	11.39	0.2780	0.2473
9	14.35	0.1400	0.2652
10	18.10	0.0395	0.1565
11	22.80	0.0081	0.0413
12	28.70	0.0071	0.0059
13	36.15	0.0058	0.0065
14	45.55	0.0000	0.0046
15	57.40	0.0000	0.0033
16	72.32	0.0000	0.0013

After corrections, the absorbance at each time, $A(T)$, was divided by the maximum absorbance, A_{max}, to obtain weight fraction dissolved at time, T, $W(DT)$. Thus, $W(DT) = A(T)/A_{max}$ and $[1 - W(DT)] = W(F)$, weight fraction undissolved at time T.

According to the Higuchi–Hiestand model for micronized range size, spherical particles dissolving under sink conditions by a diffusion controlled process the diameter, A, of a single particle at time T is given by

$$A(T) = (A_0^2 - KT)^{1/2} \qquad \text{(Eq. 1)}$$

where $A(T)$ is the diameter in centimeters at time T (sec); A_0 is the diameter at time zero; K is $(8DC)/\rho$, (cm²/sec); D is the diffusion coefficient for solute (5×10^{-6} cm²/sec); C is the solubility of solute (1.5×10^{-5} g/cm³); and ρ is the density of solute (1.3 g/cm³).

The weight fraction, $W(F)$, of a particle remaining undissolved at time T is:

$$W(F) = A(T)^3/A_0^3 = [(A_0^2 - KT)/A_0^2]^{3/2} \qquad \text{(Eq. 2)}$$

The weight fraction, $W(F)$, of multisized particles remaining undissolved at time T is:

$$W(F) = [(A_{0I}^2 - KT)/A_{0I}^2]^{3/2}(F_I) \qquad \text{(Eq. 3)}$$

where I is the channel number corresponding to the particle size range on the electronic particle size measurement instrument; A_{0I} is the initial diameter of particles in the Ith channel; and F_I is the fraction of the total volume (weight) of particles in the Ith channel.

The dissolution rate constant, K, in the above equation was varied to obtain the best fit for the dissolution profile. The calculated value for K would be $8DC/\rho = 4.6 \times 10^{-10}$ cm²/sec. Particle size distributions based on volume fraction in each channel obtained from the electronic counter were used to generate theoretical curves for $W(F)$ as a function of time.

Particle size distributions of the two small particle size fractions (fractions 1 and 2) are presented in Table I. These data represent an average of results of three experiments. Fraction 1 with the smallest particles has a mean particle diameter of 4.9 μm. Fraction 2 consists of slightly larger particles with a mean particle diameter of 7.1 μm. The narrowness of each fraction is noteworthy. For fraction 1, over 80% of the population, based on volume, is located in only 6 channels (channels 8–13), and 73% is located in only 4 channels (channels 9–12). For fraction 2, over 90% of the population, based on volume, is located in only 5 channels (channels 10–14), and 79% is located in only 3 channels (channels 11–13).

Dissolution profiles for fractions 1 and 2 are given in Fig. 1, and $W(F)$ as a function of time is plotted in this figure. Each point on these graphs represents an average of at least three experiments.

As expected, fraction 1 with smaller particles dissolves considerably faster than the one with larger particles. As can be seen from Fig. 1, almost the entire dissolution profile for each of the two fractions can be satisfactorily described by the Higuchi–Hiestand model with the dissolution rate constant, K, being 1.50×10^{-9} cm²/sec and 1.85×10^{-9} cm²/sec for fractions 1 and 2, respectively. This is ~3.5 times larger than the calculated values for K of 4.6×10^{-10} cm²/sec.

The particle size data for fractions 3 and 4 are shown in Table II. The mean for fraction 3 is 10.6 μm and the mean for fraction 4 is 13.5 μm. The narrowness for each fraction is again demonstrated with 86% of the population for fraction 1 found in 4 channels (channels 6–9), and 82% of the population for fraction 2 also found in 4 channels (channels 7–10).

Dissolution profiles for fractions 3 and 4 are presented in Fig. 2. Fraction 3, as anticipated, dissolved more rapidly than fraction 4. The dissolution profile for each fraction could be adequately described theoretically with K values of 2.0×10^{-9} and 1.7×10^{-9} cm²/sec for fractions 3 and 4, respectively. However, as with fractions 1 and 2 the K values from the experimental data are about four times larger than the theoretical value of 4.6×10^{-10} cm²/sec. It has been concluded from the previous data that the Higuchi–Hiestand model describes a relationship between particle size and dissolution rate but that the K values obtained were approximately four times the theoretical value.

DISCUSSION

It is noteworthy that the K values obtained from the dissolution profiles of four distinct narrow particle size distributions of prednisolone acetate are very similar. This finding suggests that particles ranging in average size from ~5–14 μm in diameter dissolve with one mechanism predominating. This is in keeping with the simulated data reported (7) in which it was demonstrated that a narrow distribution of drug particles, where the smallest and largest particles in the population were 2 and 20 μm in diameter, obeyed a single diffusional model. The suggestion that one mechanism predominates is further substantiated with the recognition that theory and the experimental data agree over the entire dissolution profile and not just during the initial portions of the profile.

Important to a test of this model is recognition that the shape of each experimental dissolution profile is very similar to the shape of the profile generated by the model. This observation suggests that the model is physically realistic.

While the experimental data and theory agree quite well, certain limitations must be recognized. A major finding of this study is that the theory cannot be used to predict actual dissolution profiles, since the calculated K value is ~3.5–4 times greater than the theoretical one. Part of the discrepancy may be related to the physical–chemical data used to calculate the theoretical value for K. In particular, the diffusion coefficient value is only approximate. Further, the particle size data are artificially put into discrete distribution form by the electronic counting device. The resulting histogram of particle sizes may not exactly represent the underlying distribution. However, the K value calculated in connection with Eq. 3 is dependent on the fraction of the total weight of particles in any particular channel.

As previously mentioned (2), the theory assumes that the particles are spheres, and a shape factor may account to some extent for the difference between the calculated and theoretical value for K. However, it is not expected that inclusion of a shape factor would correct for the magnitude of differences found in this study.

One other reason for the discrepancy may be related to a fundamental property of the diffusion-based model. The differential equation for the steady-state form of the model as previously used (1) is:

$$\frac{dm}{dt} = \frac{-D\Delta CA}{a} \qquad \text{(Eq. 4)}$$

where m is the weight of a solid particle, a is the particle radius at time t, and A is the area ($4\pi a^2$). Thus, one can see the similarity between this expression and the commonly used form of Fick's first law, with the particle radius, a, replacing h as the apparent diffusion layer thickness. If the value for the diffusion layer thickness was changed, albeit arbi-

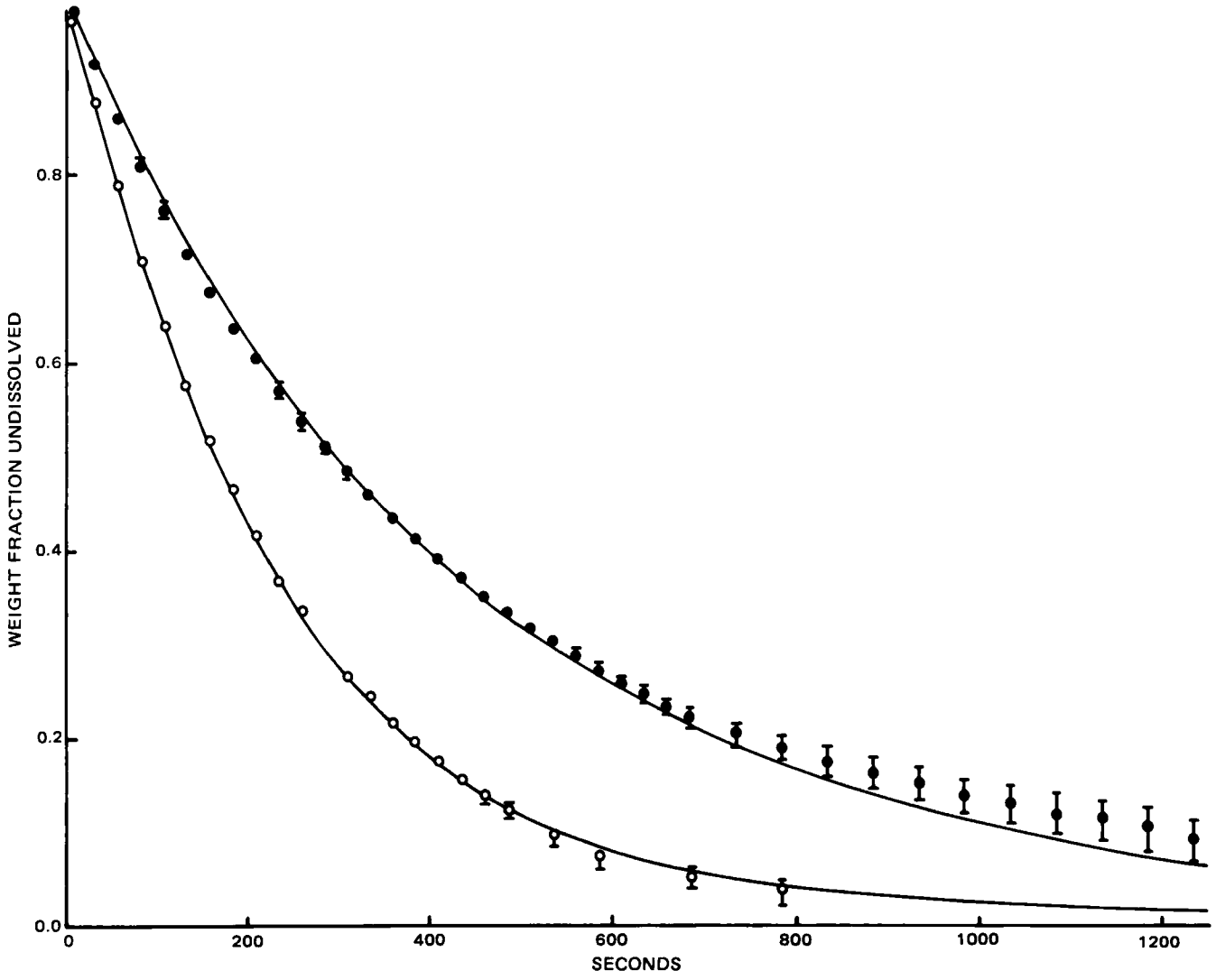

Figure 2—*Dissolution profiles for third and fourth prednisolone acetate fractions. Key: (○) experimental values for fraction 3, solid line calculated from theory with* $K = 2.0 \times 10^{-9}$ *cm²/sec; (●) experimental values for fraction 4, solid line calculated from theory with* $K = 1.7 \times 10^{-9}$ *cm²/sec.*

trarily, then the value for K calculated from the experimental data set could easily be rationalized. Unfortunately, an arbitrarily chosen proportionality constant does not provide any mechanistic insight.

The fact that the calculated value for K is greater than the theoretical one poses a question as to whether or not the diffusion layer thickness for small particles is a function of stirring. While this relationship is not predicted from convective diffusion theory for particles in the size range in this study (7), experimental verification of the actual hydrodynamic effects remains untested.

In summary, excellent correlation exists between a diffusion-based dissolution model and the experimental dissolution profiles for four narrow distributions of prednisolone acetate particles. It is noteworthy that the correlation exists over the entire dissolution profile. Similar rate constants, K, were used to fit the dissolution profile for each prednisolone acetate fraction, indicating a similar dissolution mechanism for each particle size distribution. The rate constants used to fit the experimental data are ~3–4 times greater than the theoretical rate constant calculated using independently determined or calculated values for the solute diffusion coefficient, solubility, and density.

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